State of the Science: Folic Acid 2009 **Nov. 2, 2009**

Participants: Dr. Lynn Bailey, Dr. R.J. Berry, Dr. Coleen Boyle, Dr. Richard Finnell, Dr. Paul Jacques, Dr. Richard Johnston, Dr. James Mills, Dr. Joseph Mulinaire, Dr. Godfrey Oakley, Dr. Irwin Rosenberg, Dr. Gary Shaw, Dr. Anna Maria Siega-Riz, Dr. Joe Sniezek, Dr. Patrick Stover, Dr. Edwin Trevathan, Dr. Walter Willet (by phone). (List of participant titles and affiliations is appended.)

March of Dimes Staff: Dr. Jennifer Howse, Dr. Alan Fleischman, Dr. Michael Katz, Janis Biermann, Steven Abelman, Dr. Christopher Howson, Dr. Marina Weiss

Executive Summary

The March of Dimes convened a meeting in November 2009 to examine the current state of the science on folic acid. A broad spectrum of experts in this field, including scientists, epidemiologists and public health officials, were invited to review and evaluate the current data and evidence related to folic acid fortification and its health impacts. A discussion of the following issues—1) current status of folic acid in women of childbearing age in the U.S.; 2) the benefits of folic acid; 3) the possible risks of folic acid; and 4) possible next steps—resulted in consensus on the following four recommendations:

1. **Corn masa flour fortification with folic acid in the U.S.**
   The Hispanic population in the U.S. has the highest rate of neural tube defects (NTDs). There is enough scientific evidence to support the fortification of corn masa flour with folic acid in the U.S. to reduce the racial/ethnic disparity in folic acid status by improving intake in the Hispanic population.

2. **Maintain current level of folic acid fortification of wheat flour in the U.S.**
   Data supports that folic acid fortification at the current level of 140 µg/100 g of wheat flour has resulted in a decrease in NTDs. There is no strong evidence of adverse effects due to fortification. In addition, there is not enough evidence to indicate that the level should be increased, nor would decreasing or eliminating folic acid fortification be an acceptable option, as voluntary fortification will create inequities and likely result in an increase in NTDs.

3. **Extend/enhance international efforts for folic acid fortification**
   The success of folic acid fortification programs in the U.S. and other countries such as Canada and Chile demonstrates that this effort could be effectively replicated in other countries, many of which have higher rates of NTDs. There is a moral imperative to lead the effort to expand folic acid fortification programs around the world as NTDs remain a serious, global public health problem, particularly in low- and middle-income countries.

4. **Continue additional research**
   There is need for additional research on the importance of various nutrients and vitamins on the prevention of birth defects, including the interaction between vitamin B12 and folic acid. In addition, further research is needed on the effect of folic acid on health conditions other than NTDS such as the prevention or stimulation of cancer cell proliferation, stroke and cardiovascular disease.

Meeting Summary

I. Welcome and Introductions

Dr. Fleischman reviewed the goals of the meeting as listed on the agenda:

- Review current data on folic acid in women of childbearing age in the U.S.
- Evaluate the evidence of positive and negative health impacts of folic acid education and fortification program over the last few years.
- Examine possible next steps in folic acid science and program to increase population effectiveness without causing harm.

Meeting participants introduced themselves.

Opening comments by Dr. Howse: The March of Dimes (MOD) has a rich history of participation and leadership in the area of folic acid. The MOD mission is to improve the health of babies by preventing birth defects, premature birth, and infant mortality. This resulted in a profound interest in folic acid and led to the MOD involvement in the area of folic acid:

- 1995 launch of the MOD national folic acid campaign.
- Sought fortification of the U.S. grain supply along with other organizations.
- Annual Gallup survey (first one in 1995) to measure and evaluate women of childbearing age on their knowledge and attitudes about folic acid.

Dr. Howse asked the group to share important scientific information to assist MOD in considering future policy options concerning fortification and supplementation of folic acid. The MOD will be thorough and discerning before undertaking any additional steps.

II. Issue one: The current status of folic acid in women of childbearing age in the U.S. and what we can learn from a global perspective – sources, levels, etc.

Dr. Berry Slide Presentation Summary

Summary of sources of folic acid in the adult population.

- There are both mandatory (enriched cereal grain products at 140 µg/100 g flour in the U.S. since 1998) and voluntary (ready-to-eat cereals fortified with up to 400 µg per serving since 1996 and supplements containing folic acid at ~400 µg/supplement or more).
- 2.7 % adults exceeded the tolerable upper intake level (UL) of 1,000 µg/day.
- Among women of childbearing age who did not consume supplements, only 2% achieved recommended intake of folic acid (400 µg).
- 94% of U.S. adults who do not consume supplements or consumed supplements with an average of less than 400 µg of folic acid daily are unlikely to exceed the UL. Only those who consume >400 µg/day of folic acid from supplements are likely to exceed UL.

High folate and low vitamin B12 status

- High blood folate concentrations are associated with low prevalence of vitamin B12 insufficiency and vitamin B12 level goes up as you add ready-to-eat cereals and supplements.

Dr. Bailey Comments

- Fortification has significantly increased blood folate (two-fold increase in blood folate in women aged 20-39 years between 1988-1994 and 1999-2002).

- Majority of women of reproductive age do not consume the recommended intake of folic acid, and supplement use is lower in women of reproductive age than other age categories.
- Use of supplements providing 400 µg/day is not associated with intakes exceeding the UL.

DISCUSSION

- Important to clarify that we are talking about folic acid sources, but measurements of blood levels are for folates. One of the issues to be considered is whether the targets (dietary and otherwise) should be limited to folic acid (synthetic crystalline form) which ignores folate in the diet (comes often from other forms than folic acid). As we talk about meeting targets, consider that targets should be stated in terms of folic acid intake. Upper intake level of 1000 µg is specifically stated to be for folic acid. Original requirement talked about folic acid (original 400 µg ambiguity which was referring to folate or folic acid). Discourse should include food folate as one of the inputs and the original statement by the CDC that reproductive-aged women should get 400 µg in 1992 should be revisited to see if that should be from folic acid only or include folate intake.
- In examining prevention of neural tube defects (NTDs), food folate intake was never measured because folic acid supplement intake (in addition to whatever their diet was) was easily measured. The IOM committee discussed this and recommended taking 400 µg of supplement in addition to a folate-rich diet.
- Need to consider whether NTDs are a deficiency disease or a metabolic defect/problem. If it is deficiency, 400 µg might be over what we need. If it is a metabolic defect, then may need more. Diet does matter, but early studies focused on supplements because it was measurable.
- Is there a formula to calculate the folate that comes from the diet? Group consensus from 1992 (U.S. Public Health Service) was that all the studies looked at folic acid on top of food consumption and there was variability so could not resolve this problem. Another point from 1992 was the discussion of the target dose, which was chosen based on less than optimal evidence (clinical trial by Medical Research Council/MRC for 4,000 µg and a Hungarian study recommended 800 µg). 400 µg was a compromise because those other levels of supplement were felt to be too high.
- Nutrition has played an important role historically in the prevention of NTDs. Studies from the 50s and 60s demonstrated dietary deficiencies, and a natural decline in NTDs was seen as diet got better. From 1990-1992 when you look at average intake of folate in the population, median intake was 180 to 200 µg. In 2003-2006, the median intake hasn't really changed. To change dietary folate intake would take a great deal of effort. Fortification is what made a difference in increasing blood folate and NTD prevention. However, excess is an important concern; we don't want people to get too much folic acid but the excess is coming from supplements based on Dr. Berry's presentation.
- In the U.K., they are faced with voluntary fortification. Because there could be a lot of folic acid out there that may lead to overexposure if mandatory fortification is added. What else is in the foods here? PowerBars etc.? Things like PowerBars would be in the enriched cereal grain products category. It's not listed in food tables, so we don't know whether these bars might contain high amounts, we are just making a best guess.
- The most important lesson about this whole case study of folic acid and NTDs has been a consideration of the nutritional status in the preconceptional period and an educational campaign about good nutrition during the preconceptional period. MOD has an important role in this.

III. Issue two: The benefits of folic acid on birth defects, preterm birth and other disorders.

Dr. Siega-Riz Slide Presentation Summary

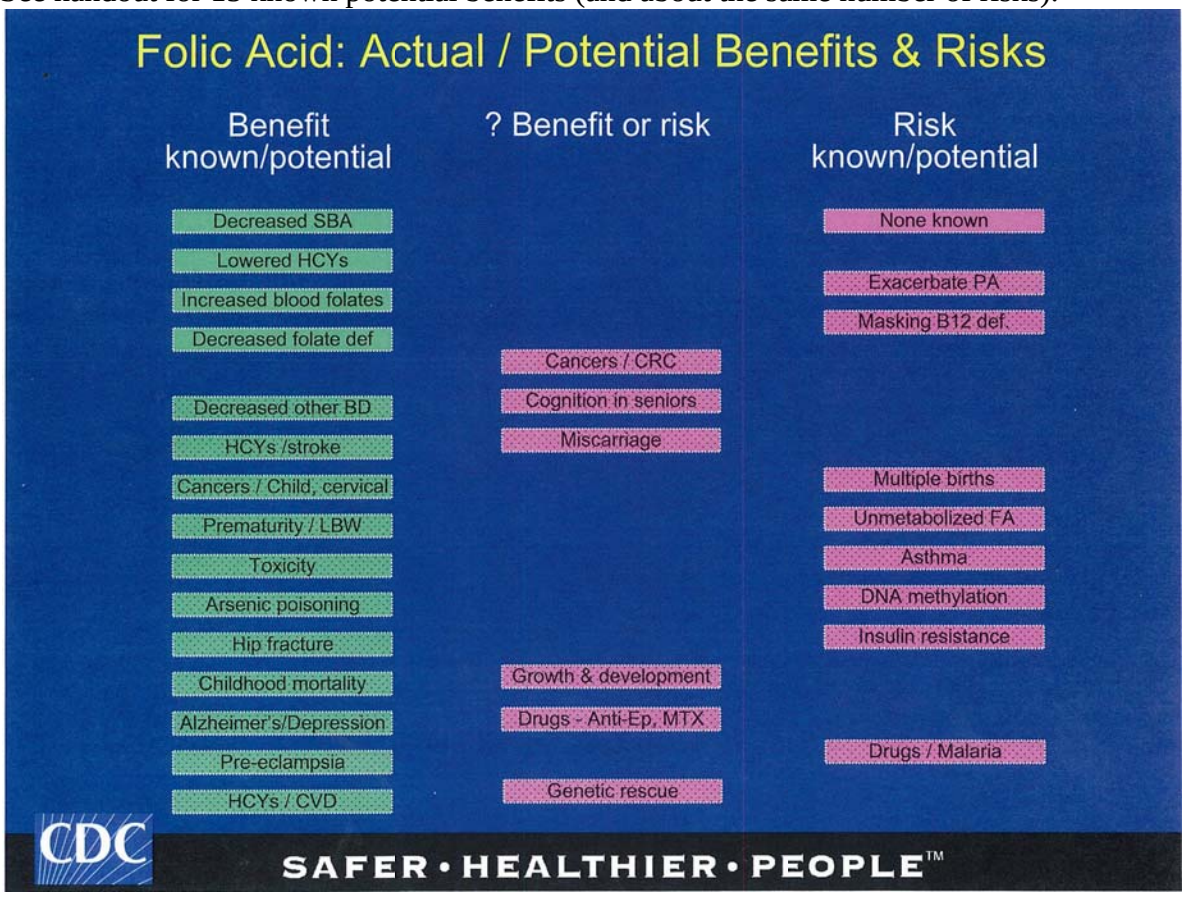
- There has been a 19% reduction in spina bifida (Honein et al., 2001)[1] due to: fortification, improved prenatal screening and diagnosis. Canfield et al. (2009)[2] showed that preconceptional folic acid use had a protective effect on spina bifida and anencephaly for Hispanic women.
- No clear link between preterm birth (PTB) and folic acid but there are some preliminary data.
  - Siega-Riz et al. (2004)[3] showed that less than optimal folate status was associated with PTB.
  - Bukowski et al. (2009)[4] examined the association between preconceptional folate supplementation and the risk of spontaneous preterm birth. The study showed the greatest benefit in those who took folic acid for more than one year. A decrease in the risk for spontaneous PTB was seen in those born at less than 32 weeks, but result could be associated with other healthy behaviors (not a randomized controlled trial).
- Very small if any effect on twinning.
  - Cochrane review (2001)[5] found a negative effect.
  - Signore (2005)[6] looked at twinning after fortification in the U.S. in older women (more likely to be getting assisted reproductive technology/ART) and young women (less likely to be getting ART). There was only a slight increase post fortification in twin gestation rates in both groups.
- Inconsistent effect on cancer
  - Mason et al. found (2007)[7] increased incidence of certain cancers (e.g., colorectal) seen right around the period of fortification in the U.S. and Canada. However, increased screening is a potential explanation for this.
  - Fife et al. (2009)[8] meta-analysis found no overall increased risk of adenoma and advanced adenoma at less than 3 years follow-up, though saw somewhat of an increase after 3 years.
  - Zhang et al. (2008)[9]: There was no significant effect on overall risk of total invasive cancer or breast cancer during the folic acid fortification era.
  - Hirsch et al. (2009)[10]: Increase in colon cancer rates in Chile after fortification (200 µg/100 g wheat flour).

Dr. Shaw Comments

[1] Honein MA, Paulozzi LJ, Mathews TJ, Erickson JD, Wong LY. Impact of folic acid fortification of the US food supply on the occurrence of neural tube defects. JAMA 2001;285:2981-6.
[2] Canfield MA, Ramadhani TA, Shaw GM, et al. Anencephaly and spina bifida among Hispanics: maternal, sociodemographic, and acculturation factors in the National Birth Defects Prevention Study. Birth Defects Res A Clin Mol Teratol 2009;85:637-46.
[3] Siega-Riz AM, Savitz DA, Zeisel SH, Thorp JM, Herring A. Second trimester folate status and preterm birth. Am J Obstet Gynecol 2004;191:1851-7.
[4] Bukowski R, Malone FD, Porter FT, et al. Preconceptional folate supplementation and the risk of spontaneous preterm birth: a cohort study. PLoS Med 2009;6:e1000061.
[5] Lumley J, Watson L, Watson M, Bower C. Periconceptional supplementation with folate and/or multivitamins for preventing neural tube defects. Cochrane Database Syst Rev 2001:CD001056.
[6] Signore C, Mills JL, Cox C, Trumble AC. Effects of folic acid fortification on twin gestation rates. Obstet Gynecol 2005;105:757-62.
[7] Mason JB, Dickstein A, Jacques PF, et al. A temporal association between folic acid fortification and an increase in colorectal cancer rates may be illuminating important biological principles: a hypothesis. Cancer Epidemiol Biomarkers Prev 2007;16:1325-9.
[8] Fife J, Raniga S, Hider PN, Frizelle FA. Folic Acid Supplementation and Colorectal Cancer Risk; A Meta-analysis. Colorectal Dis 2009.
[9] Zhang SM, Cook NR, Albert CM, Gaziano JM, Buring JE, Manson JE. Effect of combined folic acid, vitamin B6, and vitamin B12 on cancer risk in women: a randomized trial. JAMA 2008;300:2012-21.
[10] Hirsch S, Sanchez H, Albala C, et al. Colon cancer in Chile before and after the start of the flour fortification program with folic acid. Eur J Gastroenterol Hepatol 2009;21:436-9.

- There are other studies that indicate that other nutrients beyond folic acid play a role in possibly preventing NTDs. Metabolism of folic acid is complicated and other nutrients can play a role.
  - Wald et al. (1991)[11]: The original MRC trial was stopped before a significant association could be achieved for the arm that didn't involve folic acid.
  - Molloy et al. (2009)[12]: As vitamin B12 serum levels go down, risk of NTDs go up independent of folate.
  - Choline (Dr. Shaw's study): As choline levels in serum go up, risk of NTDs goes down in a linear construct.

Dr. Mulianire Comments
See handout for 15 known potential benefits (and about the same number of risks).



DISCUSSION

- We should be careful not to over-interpret these possible benefits of folic acid.
  - Cardiovascular disease (CVD) effects are complicated, stroke is supported by evidence.
  - For cancer, there seem to be benefits with long-term folate supplementation with colon cancer.
  - No evidence that folic acid prevents NTDs in situations where people take other drugs (anticonvulsants) like valproic acid. There's no solid evidence that the

[11] Prevention of neural tube defects: results of the Medical Research Council Vitamin Study. MRC Vitamin Study Research Group. Lancet 1991;338:131-7.
[12] Molloy AM, Kirke PN, Troendle JF, et al. Maternal vitamin B12 status and risk of neural tube defects in a population with high neural tube defect prevalence and no folic acid fortification. Pediatrics 2009;123:917-23.

antifolate effects of drugs such as anticonvulsants would be blunted or prevented by folic acid.
    - Within the neurology community, we have not been seeing increased masking of pernicious anemia with fortification.
- "Floor" effect of folic acid fortification in preventing NTDs. What is the floor for the maximal benefit of folic acid?
    - Concept of looking at rate rather than percentage decline. Getting down to a number such as 6 or 7 NTDs per 10,000 births may be a floor effect. Going below that may not be possible with folic acid.
    - Need to be careful about establishing what the floor rate is. Live births as denominator will look low and will miss some NTDs from terminations.
    - Chilean data would be extremely informative since there's lack of terminations. Lowest seen is 8 in 10,000 but not published, anecdotal.
    - Floor might be specific to populations, can't look for one universal one.
    - What is the impact of prenatal screening on the 19% decrease in the overall prevalence rate of NTDs (from Honein et al., 2001)[13]? If you look at the National Birth Defects Prevention Network (NBDPN) comparison of state surveillance systems with and without prenatal ascertainment in 1995-1996 and 2005-2006 rates, see 40% reduction in the prenatal ascertainment states. The percentage of 40% that is due to change in folic acid fortification is complicated. Honein's data were from vital statistics which includes only live births. Data from NBDPN is a combination of prenatal diagnoses as part of the rate (some states do, and others don't) and that is about 40%. See page 189 from unpublished book chapter Berry RJ et al., (2009)[14]. Williams et al. (2002)[15] study shows 9 states with prenatal ascertainment for spina bifida had an increase in percent decline.
- There are unresolved issues regarding vitamins, vitamin B12 nor choline were in MRC trials, and there are no studies following up on vitamin C. Choline is interesting because you're looking at methyl groups and metabolism in the folate pathway.
- There's little data on folic acid and prematurity. What are your impressions? Prematurity rate is flat below 32 weeks postfortification so it's not a very strong argument. It's hard to isolate folic acid for prematurity.
- Other birth defects helped by folic acid include cleft lip, some heart defects, urinary tract defects, and diaphragmatic hernia.
    - These are observational studies, need a randomized controlled trial (RCT) along the lines of Czeizel study[16] of cardiovascular defects with multivitamins.
    - Neural crest effects seem to be the common denominator.
- Need more studies looking at stroke and folic acid. Individual trials don't show benefit, some meta-analysis has.
    - There was a study in China that showed a reduction in stroke with folate supplementation, but they have more folate deficiency there. Need to do these studies in places with low folate status.
- It is important to do a randomized controlled trial. If the use of folic acid is not randomized, it is hard to tease out useful information.

[13] Honein MA, Paulozzi LJ, Mathews TJ, Erickson JD, Wong LY. Impact of folic acid fortification of the US food supply on the occurrence of neural tube defects. JAMA 2001;285:2981-6.
[14] Berry RJ, Mulinare J, Hamner HC. Folic Acid Fortification: Neural Tube Defect Risk Reduction-A Global Perspective. In: Bailey L, editor. Folate in Health and Disease, 2nd Edition, 2009.
[15] Williams LJ, Mai CT, Edmonds LD, et al. Prevalence of spina bifida and anencephaly during the transition to mandatory folic acid fortification in the United States. Teratology 2002;66:33-9.
[16] Czeizel AE. Reduction of urinary tract and cardiovascular defects by periconceptional multivitamin supplementation. Am J Med Genet 1996;62:179-83.

IV. Issue Three: The possible risks of folic acid—what do we know about cancer, the aging population, free folic acid, high folic acid, low B12 etc.

Dr. Stover Slide Presentation Summary

- Mechanism of folate preventing NTDs and folate-cancer relationship are unknown.
- Biological activity of folic acid.
  - Folate is chemically unstable, but folic acid is chemically stable, highly bioavailable, synthetic and does not accumulate in the cell. It's reduced to natural folate in cells.
  - Folic acid does not accumulate in cells. Folic acid gets into cells via receptors then it is converted to natural folate and receives a folate polyglutamate chain, otherwise it will be pumped out of cells.
  - There are more folate enzymes than there is folate – network is competing for folate and disruption of this network can cause issues relating to BDs.
  - Kelly et al. (1997)[17]: Differing levels of free folic acid levels measured in serum. At higher levels of folic acid, folic acid was detected in the serum. This might mean that the system is saturated at about 400 µg.
  - Bailey et al. (2009)[18] looked at livers of rats. There was high degree of heterogeneity in the activity of dihydrofolate reductase (DHFR, an enzyme in the folic acid pathway), this may account for differences in saturation. Variation in population could explain difference in people.
  - Troen et al. (2006)[19] examined the potential adverse effect of excessive folic acid intake by evaluating intake of folic acid in relation to an index of immune function (natural killer cell cytotoxicity, important in fighting viral infections and can also kill cancer cells) in postmenopausal women. Unmetabolized folic acid was detected in 78% of participants and there was an association between unmetabolized folic acid in plasma and decreased natural killer cell cytotoxicity. Need more studies to understand mechanism and relationship between folate metabolism and immune function.
- Elevated folate status and vitamin B12 deficiency interactions, masking the diagnosis of vitamin B12 deficiency.
  - Elevated folate may exacerbate effects of vitamin B12 deficiency, as first suggested in the IOM report in 1998. Functional vitamin B12 deficiency may be common and is often undiagnosed, but no studies show causality.
  - Selhub et al. (2007)[20] looked at serum vitamin B12 data and found that increased folate is associated with increased homocysteine levels.
  - In vitamin B12 metabolism, the terminal step is the only place where vitamin B12 and folate interact so there is no good explanation for how this happens.
  - Morris et al. (2007)[21]: In seniors with low vitamin B12, high serum folate was associated with anemia and cognitive impairment. There is a functional relationship but the basis is unclear.
  - Folic acid masking vitamin B12 deficiency is not an issue.

[17] Kelly P, McPartlin J, Goggins M, Weir DG, Scott JM. Unmetabolized folic acid in serum: acute studies in subjects consuming fortified food and supplements. Am J Clin Nutr 1997;65:1790-5.

[18] Bailey SW, Ayling JE. The extremely slow and variable activity of dihydrofolate reductase in human liver and its implications for high folic acid intake. Proc Natl Acad Sci U S A 2009;106:15424-9.

[19] Troen AM, Mitchell B, Sorensen B, et al. Unmetabolized folic acid in plasma is associated with reduced natural killer cell cytotoxicity among postmenopausal women. J Nutr 2006;136:189-94.

[20] Selhub J, Morris MS, Jacques PF. In vitamin B12 deficiency, higher serum folate is associated with increased total homocysteine and methylmalonic acid concentrations. Proc Natl Acad Sci U S A 2007;104:19995-20000.

[21] Morris MS, Jacques PF, Rosenberg IH, Selhub J. Folate and vitamin B-12 status in relation to anemia, macrocytosis, and cognitive impairment in older Americans in the age of folic acid fortification. Am J Clin Nutr 2007;85:193-200.

- Cancer: Acceleration of growth of established neoplastic clones.
  - In Cole et al. (2007)[22], folic acid did not reduce colorectal adenoma risk. Folic acid was associated with higher risks of having 3 or more adenomas and non-colorectal cancers.
  - Zhang et al. (2008)[23] found that supplementation with folic acid, vitamin B6 and vitamin B12 had no effect on overall risk of invasive cancer or breast cancer in the postfortification period.
  - Wu et al. (2009)[24] found that the folic acid supplementation group with low plasma folate concentrations at baseline had a significant decrease in adenoma recurrence. There was no evidence of increased risk of advanced or multiple adenomas in the folic acid group.
- Reproductive outcomes including epigenetic programming, folic acid for human miscarriage prevention, multiple births.
  - Elevated levels of folic acid might affect epigenetic programming, Folate is important in methylation reactions at the level of the genome. Persistent effects of B vitamin nutrition are shown by rat coat color being affected by maternal expression of the gene influenced by diet. Color persisted into adulthood regardless of the diet of the offspring.
  - Low maternal protein results in low birthweight, hypertension, and hyperglycemia. You can prevent gene programming if you give elevated levels of folic acid in the rodent diet.
  - Relationship between nutrition and epigenetic programming is not clear: Pune Maternal Nutrition Study found indicated risk of insulin resistance in children born from mothers who consumed folic acid supplement with low vitamin B12 and elevated folate status but a recent RTC study in Nepal did not confirm this finding.
  - Miscarriage prevention: A number of genes play a role in maternal or fetal risk of miscarriage. Several studies tested this hypothesis but there is no evidence that folic acid can rescue spontaneous abortions.

Dr. Mills Slide Presentation Summary

- Does folic acid promote malignancies?
  - Mixed data from clinical trials do not resolve the issue, historical data indicate that folic acid promotes cancer growth.
- Masking vitamin B12 deficiency.
  - Limited data do not show a risk at current fortification levels.
- What does unmetabolized folic acid do?
  - Present in blood for prolonged period in supplement takers. It does enter at least some cells (particularly liver).
- How does unmetabolized folate enter pathway or cause imbalance?
  - Folate and folic acid enter the pathway at different points. Food folate goes into both pathways but folic acid only goes into one. Normal balance could be shifted by having extra folic acid.
- Studying cells in research is different than *in vivo* (e.g., receptors are different).

[22] Cole BF, Baron JA, Sandler RS, et al. Folic acid for the prevention of colorectal adenomas: a randomized clinical trial. JAMA 2007;297:2351-9.
[23] Zhang SM, Cook NR, Albert CM, Gaziano JM, Buring JE, Manson JE. Effect of combined folic acid, vitamin B6, and vitamin B12 on cancer risk in women: a randomized trial. JAMA 2008;300:2012-21.
[24] Wu K, Platz EA, Willett WC, et al. A randomized trial on folic acid supplementation and risk of recurrent colorectal adenoma. Am J Clin Nutr 2009;90:1623-31.

Dr. Jacques Presentation Summary

- There is limited data on risk.
- Unmetabolized folic acid and circulating folate – confounding in people with high levels due to folic acid (not from diet) and high correlation with circulating folic acid levels and plasma levels. Teasing out risk of folate versus folic acid will be very difficult.
- One reason circulating folate has increased postfortification is that one is exposed to folic acid throughout the day as opposed to a supplement once a day. Metabolism to remove folic acid might be changed—clearance could be affected and different postfortification.
- U-shaped association with cancer risk—there is substantial evidence that higher folate will prove protective, and hopefully will see this protective effect down the road with colon cancer.
- Folate-vitamin B12 interaction: Argue against the possibility that impaired absorption is causing this. This is seen across the whole range with the exception of the lowest level.

DISCUSSION

- Not all cells have folate receptors but all cancer cells do. Some of the data may be influenced by this fact.
- How does folic acid or folate interact with certain cells and transporters? Transporters in the brain are different than those in the gut. Transporters in the brain have a high affinity for folic acid, but we are not sure how effective it is in transporting folic acid. There could possibly be a competition between folic acid and folic methylase.
  - Ability of folate to get into the brain is a black box. Have at least 2,000 SNPs in the folic metabolic pathway that that is going to inform what receptor is it is dealing with at any given time.
- Regarding vitamin B12-folate interaction, are we going to be doing something good for women of childbearing age by putting older people at risk? Whether this is an expression of malabsorption or other things, we do have a phenomenon for vitamin B12-folate interaction that is more likely to be adverse in the elderly.
  - Why aren't these people who are likely to have early/pre-pernicious anemia being treated early? If someone has symptoms they should be tested. Almost all these people are receiving multivitamins containing vitamin B12. If you take a multivitamin and your vitamin B12 levels are low, you should be tested for the deficiency. There could be a screening system for anyone over 50 years old.
  - High folate acts as a filter/marker for people who are getting folate, high levels of vitamin B12 and not getting treated. The ones who could be treated are treated, and there is a residual there and that is a natural screening test that could be a marker to investigate that person for vitamin B12 deficiency.
- Every prenatal has closer to 1 mg in it so every person born in this country in the last 50 years has been exposed to free-floating folic acid. Folate is transported across the placenta. A fetus has three times the folate concentration in serum level across the whole range. Both folate and folic acid could be bound and transported from mother to fetus.
  - Based on the amount of folic acid women are getting, this folic acid is being converted to methylfolate. It's rare that we see people postfortification with inadequate folate levels. Factors independent of folate will affect the floor, e.g., environmental or genetic factors Different tissues respond differently in their sensitivity to folate.

V. Issue Four: Looking forward—possible next steps in birth defects prevention

Dr. Johnston Slide Presentation Summary
Possible next steps include the following:

1) Education

Able to target consumer groups (e.g., young women & elderly), but there's limited effectiveness and concerns about unmetabolized folic acid.

2) Extend folic acid fortification internationally.

While we may be able to prevent many thousands of NTDs, there are governmental challenges.

3) Add folic acid into corn masa flour in U.S.

This would target the Hispanic population, which has the highest NTD rates in U.S. but could face procedural barriers. FDA categorizes corn masa flour differently and would not consider folic acid fortification when the issue was raised about 3 years ago.

4) Maintain current folic acid fortification levels in the U.S.

There's proven benefit and no proven adverse effects, requires no new effort.

5) Increase folic acid fortification in U.S.

If so, how much? And in addition to fortifying corn masa flour, or possibly limit level of voluntary folic acid fortification? It may or may not prevent more NTDs and there's uncertainty regarding some adverse effects.

6) Eliminate mandated folic acid fortification in U.S. and allow voluntary folic acid fortification of grains.

This removes the question of risk and need for research on risks but thousands of lives would be negatively affected by preventable NTDs.

7) Explore addition of vitamin B12 regardless of what is done with folic acid fortification.

This could address an important need in elderly and could increase NTD prevention but means additional expenses and a need for involvement of advocates for the elderly.

8) Push for targeted research.

Topics include:

- Effect of any change in folic acid fortification on NTD rates, beneficial and adverse effects.
- Effect of total folic acid intake on beneficial effects – cancer, other BDs dementia, cardiovascular disease.
- How does folic acid prevent NTDs?
- Susceptibility polymorphisms/genes.

Dr. Willet Comment Summary

- Fortification – Suggest staying on course with what we are currently doing. No clear evidence of harm.
- Birth defects – Explore if there are other nutrients that may be contributing to lower risk
    - Incidence of folic acid preventable NTDs is close to reaching the floor, so it will be hard to detect in subgroups.
    - Further epidemiologic studies around NTDs will be useful but they will need to be large studies (case control will be problematic, cohort studies preferable with different designs than before). Nordic cohorts might be big enough. A study looking

at cases of NTDs in a fortified area taking a multivitamin and looking at genetics would be an interesting case due to possible genetic abnormalities present.

- The issue of cancer incidence in relation to folic acid needs further follow-up. Colon cancer diagnosis has increased but this corresponded with a switch in type of testing done. Cancer epidemiology is embryonic, will need more data further down the road.
- The discussion of vitamin B12 seems to indicate a positive effect on cognitive function.
  - Need to understand more and sort out whether higher intake of vitamin B12 is really useful. If so, how much more? However, now is not the time to fortify with vitamin B12 until more studies are done.
- There's some concern about supplements in addition to fortification. It is possible that the current level of folic acid in supplements doesn't need to stay at that level.

DISCUSSION

Based on the discussion, the group came to a consensus on the following next steps:

1. **Corn masa flour fortification with folic acid in the U.S.**

   The Hispanic population in the U.S. has the highest rate of NTDs. A 2009 study published by the NCBDDD group of the CDC (Hamner et al., 2009[25]) used data from the National Health and Nutritional Examination Survey (NHANES) to develop a model to calculate the potential effects of fortifying corn masa flour with folic acid in the U.S. It was found that theoretical corn masa flour fortification would increase the intake of total daily folic acid in Mexican American women of childbearing age by 19.9% (compared to 4.2% in non-Hispanic white women). With this model, Mexican American women were estimated to have median usual daily intakes much closer to those reported by non-Hispanic white women, despite a higher prevalence of supplement use among non-Hispanic white women. Corn masa flour has already been fortified in some countries (e.g., Mexico, Guatemala, Costa Rica, and South Africa) although the group did not know of any data to document success.

   The group agreed that there was enough scientific evidence to support the fortification of corn masa flour with folic acid in the U.S. to reduce the racial/ethnic disparity in folic acid status and incidence of NTDs by improving intake in the Hispanic population. The group briefly discussed the possible implementation/procedural issues with the FDA as a possible barrier, but agreed that an effort should be initiated.

2. **Maintain current level of folic acid fortification of wheat flour in the U.S.**

   The group agreed that the current level of folic acid fortification at 140 µg/100 g of wheat flour was adequate, as it has been proven to reduce the incidence of NTDs and there is no strong evidence of adverse effects due to fortification. In addition, there is not enough evidence to indicate that the level should be increased, nor would decreasing or eliminating folic acid fortification be an acceptable option, as voluntary fortification will create inequities and likely result in an increase in NTDs. There was some discussion about whether the U.S. had reached the point where all preventable NTDs had been prevented, and the need to monitor and continue research to clarify whether there are any risks before moving forward.

3. **Extend/enhance international efforts for folic acid fortification**

There were approximately 324,000 births affected by neural tube defects (NTDs) around the world in 2001 (March of Dimes Global Report on Birth Defects, 2006), underscoring the seriousness of the international problem with NTDs. The success of folic acid fortification

[25] Hamner HC, Mulinare J, Cogswell ME, et al. Predicted contribution of folic acid fortification of corn masa flour to the usual folic acid intake for the US population: National Health and Nutrition Examination Survey 2001-2004. Am J Clin Nutr 2009;89:305-15.

programs in the U.S. and other countries such as Canada and Chile demonstrates that this effort could be effectively replicated in other countries, many of which have higher rates of NTDs. The group agreed that there is a moral imperative to lead the effort to expand programs around the world as NTDs remain a serious, global public health problem, particularly in low- and middle-income countries.. As there are other competing public health issues that some of these countries deal with, it may help to have economic analysis that could speak to policy/decision makers in these countries that show benefits of fortification for NTDs and also the cost of doing nothing.

4. **Continue additional research**
   Throughout the meeting, the group emphasized the need for additional research, particularly related to potential risks that folic acid may pose on other health conditions.
   - Vitamin B12 and folic acid: The interaction between vitamin B12 and folic acid needs to be further elucidated.
   - Cancer: Overall data points to no significant/harmful effect or a likely reduction for various cancers but need more research to clarify previous findings.
   - Stroke: Individual trials haven't shown a benefit, although some meta-analysis has. Studies need to be done in places with low folate status to show a clear result (e.g., study in China showed a reduction in stroke with supplementation).
   - Other nutrients: Nutrients beyond folic acid may play a role in preventing NTDs, such as choline.

Other issues discussed but general consensus was not reached:

- **Improving educational efforts:** The group discussed targeting education for health care professionals. Health care professionals are aware of folic acid but they may not mention it in their encounters with women of reproductive age. There was a suggestion to incorporate it as a question in the electronic medical records for the annual well-woman exam so it is more systematic. There was also a suggestion to target elementary/middle/high school for early education about folic acid. Encouraging women of childbearing age to eat a healthy diet (to counter low-carbohydrate diets and obesity) rich in carbohydrates and fruits/vegetables was also mentioned. One problem with this is that if women were to consume more nutrient-rich carbohydrates (which are not fortified), they may not be consuming as much folic acid as if they were to consume more refined starches (which are fortified with folic acid).
- **Vitamin B12 Fortification:** The group discussed the possibility of fortification of grains with vitamin B12 for further enhancing the prevention of NTDs and possibly neurological complications in the elderly population. Studies are needed to clarify this relationship and to figure out what the appropriate fortification level would be.
- **Target/metrics for NTD eradication:** It was suggested to try to establish a metrics that can be used to measure eradication of folic acid preventable NTDs. Two researchable issues are whether the currently recommended 400 µg is the right number, and what the target number for the NTD rate should be (as in x per 10,000 in the population instead of a percentage reduction).